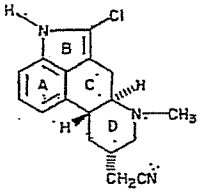
EXHIBIT H

Proposed Dopaminergic Pharmacophore of Lergotrile, Pergolide, and Related Ergot Alkaloid Derivatives

Sir:

The central dopamine agonist properties of certain derivatives of ergot alkaloids, typified by lergotrile (1) and



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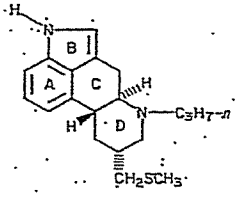

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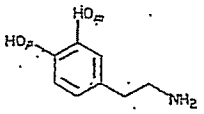

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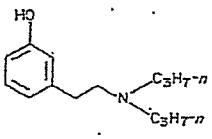
pergolide (2), have been well documented in the literature.[1,2] Marek and Roth[3] stated that 1 is a potent agonist at presynaptic dopamine receptors on striatal and mesolimbic nerve terminals. Goldstein et al.[4] concluded that lergotrile has the properties in the CNS of a mixed agonist–antagonist with respect to some presynaptic dopamine receptors. However, there seems to be little structural resemblance between 1 and 2 and dopamine (3), and a reviewer[5] stated in 1978 that ergot alkaloids bear little structural resemblance to the dopaminergic aporphines and 2-aminotetralins.

In 1978, one of us[6] suggested that lergotrile is related structurally to dopamine, if it is accepted that the weakly acidic indole NH group is bioisosteric with the "meta" OH of dopamine. The meta OH has been proposed[7] to be of considerable importance in agonist–receptor interaction. Some support is given to this proposal by the report of Geissler[8] that *N,N*-di-*n*-propyl-*m*-tyramine (4) has dop-



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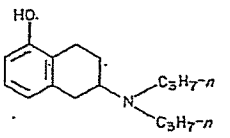

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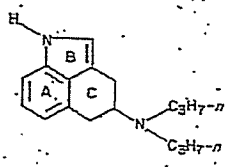
amine agonist actions and the report of McDermed et al.[9] that 2-(di-*n*-propylamino)-5-hydroxytetralin (5) is a potent dopaminergic. Bach and Kornfeld[10] described the ergoline fragment 6 and stated that it inhibited prolactin secretion



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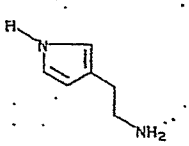

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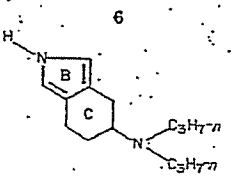

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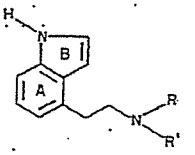

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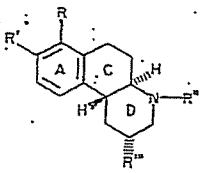

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and dopamine binding, which are characteristic actions of dopaminergic agonists. Bach et al.[11] found that 3-(2-aminoethyl)pyrrole (7) was ineffective in lowering prolactin levels, which was attributed to rapid metabolic inactivation of the primary amine by monoamine oxidase. No tertiary amine derivative of 7 was reported. Compound 8, a BC bicyclic ergoline partial structure, exhibited prolactin-inhibitory activity, as well as some activity in a rat rotation assay, albeit in high doses in both assays. Bach et al.[12] have reported that depyrroloergolines (10, R = R′ = H; R″ = *n*-C_3H_7; R‴ = CH_2SCH_3) are dopaminergically inactive in two tests. In contrast, catechol derivatives of 10 (R = R′ = OH; R″ = alkyl; R‴ = H) are highly active, potent dopaminergics.[5]

Inspection of the molecular structures of lergotrile (1) and pergolide (2) suggested that the pharmacophore of lergotrile, pergolide, and 6 may be a 4-(2-aminoethyl)indole system, 9. Hofmann and Troxler[13] described derivatives of 9 (R, R′ = H, Me) and suggested that these "could be used in treatment of asthma". However, the literature has not revealed that they have been evaluated for dop-

(1) McDermed, J.; Miller, R. J. *Annu. Rep. Med. Chem.* 1979, *14*, 12.
(2) Fuller, R. W.; Clemens, J. A.; Kornfeld, E. C.; Snoddy, H. R.; Smalstig, E. B.; Bach, N. J. *Life Sci.* 1979, *24*, 375.
(3) Marek, K. L.; Roth, R. H. *Eur. J. Pharmacol.* 1980, *62*, 137.
(4) Goldstein, M.; Lew, J. Y.; Nakamura, S.; Battista, A. F.; Lieberman, A.; Fuxe, K. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1979, *37*, 2202.
(5) McDermed, J.; Miller, R. J. *Annu. Rep. Med. Chem.* 1978, *13*, 11.
(6) Cannon, J. G. In "Peripheral Dopaminergic Receptors"; Imbs, J.-L.; Schwartz, J., Eds.; Pergamon Press: New York, 1979; pp 87–94.
(7) Cannon, J. G. *Adv. Neurol.* 1975, *9*, 177.
(8) Geissler, H. E. *Arch. Pharm. (Weinheim)* 1977, *310*, 749.
(9) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* 1976, *19*, 547.
(10) Bach, N. J.; Kornfeld, E. C. U.S. Patent 4 110 339, 1978; *Chem. Abstr.* 1979, *90*, 121415*f*.
(11) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* 1980, *23*, 481.
(12) Bach, N. J.; Kornfeld, E. C.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* 1980, *23*, 812.
(13) Hofmann, A.; Troxler, F. French Patent 1 344 579, 1963; *Chem. Abstr.* 1964, *60*, 11988.

Table I. Sympathetic Neuronal Inhibiting Activity of Lergotrile (1), Pergolide (2), and 4-[2-(Di-*n*-Propylamino)ethyl]indole (9) in Anesthetized Cats

no.	dose, μg/kg	% inhibn of cardioaccelerator nerve stimulation, 2 Hz	inhibitory effect reversed by haloperidol, 100 μg/kg	ID_{50}, μmol/kg (95% CL)	potency ratio[a] rel to apomorphine (fiducial limits)
1	30	21 ± 7	yes, $p < 0.01$, $n = 5$	0.27 (0.13–0.62)	0.08 (0.04–0.16)
	100	57 ± 12			
	300	69 ± 10			
2	3	23 ± 3	yes, $p < 0.01$, $n = 7$	0.02 (0.01–0.02)	1.13 (0.7–1.8)
	10	59 ± 6			
	30	80 ± 5			
9	30	29 ± 10	yes, $p < 0.01$, $n = 7$	0.22 (0.12–0.33)	0.14 (0.07–0.33)
	100	60 ± 4			
	300	77 ± 8			

[a] Apomorphine was used as a reference dopamine agonist inhibiting the positive chronotropic response induced by stimulation of the right cardioaccelerator nerve at 2-Hz frequency.

amine-like effects. In the present work, the target compound based on 9 bears *n*-propyl groups on the side-chain amino group, consistent with several reports[6] that this N-substitution tends to maximize dopaminergic activity and potency.

Synthesis of 9 (R = R′ = *n*-C_3H_7) began with a Reissert indole sythesis using 6-chloro-2-nitrotoluene. The 4-chloroindole product was converted into 4-cyanoindole with $Cu_2(CN)_2$.[14] This nitrile was hydrolyzed to indole-4-carboxylic acid, and the *N*-benzoyl derivative of this acid was homologated to indole-4-acetic acid by an Arndt–Eistert sequence. This carboxylic acid was converted to its *N*,*N*-di-*n*-propylamide with di-*n*-propylamine and hexamethylphosphorous triamide/CCl_4. The amide was reduced with $LiAlH_4$ to 9 (R = R′ = *n*-C_3H_7), which was characterized and evaluated biologically as its bifumarate salt, mp 154–155 °C (EtOH–Et_2O–petroleum ether): MS, *m/e* 244 (M^+ – fumaric acid).

Pharmacology. Methods. Inhibition of Postganglionic Cardioaccelerator Nerve in Cats. Anesthesia was induced by intrathorax administration of pentobarbital sodium (30 mg/kg). Arterial pressure was measured from the right femoral artery using a Statham P23AA pressure transducer and was recorded using a Beckman RS dynograph. The pulses were integrated and recorded by use of a cardiotachometer. The respiration was supported by a Harvard respiratory pump and, following a midline incision of the thorax, bipolar platinum electrodes were placed on the right postganglionic cardioaccelerator nerves for stimulation using a Grass S4S stimulator. The frequency of stimulation was 2 Hz. The impulses were delivered from 20–30 s and a pulse duration of 5 ms was used. Supramaximal voltage was used. After the establishment of consistent controls, 1, 2, or 9 was administered to cats in doses that varied by 0.48 log intervals. The ability of 1, 2, and 9 to affect mean arterial pressure and resting heart rate was determined, as well as the ability to inhibit neuronal sympathetic transmission. At the completion of each experiment, 100 μg of haloperidol was administered iv, and the ability of the compounds to inhibit cardioaccelerator nerve stimulation was redetermined.

Inhibition of Spontaneous Locomotion in Rats. Sprague–Dawley rats (225–250 g) were kept in a lighted room for at least 24 h. Pairs of rats were injected sc with 9 (R = R′ = *n*-C_3H_7) and placed in a darkened room for 30 min and then in a *Plexiglas* container, and locomotion was followed using an electromagnetic activity meter (Columbus Instruments, Model S) for an additional 30 min. The counts recorded during the first 6 min were discarded, and the following 24-min counts were recorded. Six pairs of rats were used for each dose and received either saline (0.9%) or 0.33, 1.0, or 3.3 mg/kg 9 in normal saline.

Renal Vasodilatation Experiments in Dogs. The standard procedure of Goldberg[15] was used for studying the vascular (postsynaptic) effects of the compounds. Pentobarbital-anesthetized dogs were prepared for recording carotid blood pressure and renal artery flow. Various doses of the compounds and dopamine were injected intraarterially in a fixed volume of 0.2 mL.

Statistics. The ID_{50} values for inhibition of cardioaccelerator nerve stimulation and inhibition of locomotion were calculated by the method for probit analysis, and bioassays were analyzed by parallel line assay as described by Finney.[16]

Results and Discussion

The presence of presynaptic dopaminergic receptors inhibiting sympathetic transmission has been well documented.[17] Many compounds possessing dopamine-like properties have been shown to inhibit the positive chronotropic response induced by low-frequency nerve stimulation.[18–23] This neuronal activity involves the stimulation of presynaptic dopaminergic receptors present in the peripheral sympathetic nerve endings, resulting in a decrease of norepinephrine release, an effect blocked by dopamine antagonists. This has been used as a tool for detecting compounds exerting dopaminergic activity.

All of the compounds studied elicited significant dopaminergic activity. Table I shows that lergotrile (1) and 9 were equally active in anesthetized cats in a test for their ability to inhibit neuronal postganglionic cardioaccelerator nerve stimulation. Pergolide (2) was the most active in

(14) Uhle, F. C. *J. Am. Chem. Soc.* 1949, *71*, 761.
(15) Goldberg, L. I.; Volkman, P. H.; Kohli, J. D. *Annu. Rev. Pharmacol. Toxicol.* 1978, *18*, 57.
(16) Finney, D. J. "Statistical Methods in Biological Assays"; Griffin: London, 1952; pp 139–145.
(17) Langer, S. Z. In "Presynaptic Receptors"; Langer, S. Z.; Starke, K.; Dubocovich, M. L., Eds.; Pergamon Press: New York, 1979; pp 13–22.
(18) Ilhan, M.; Long, J. P.; Cannon, J. G. *Eur. J. Pharmacol.* 1975, *33*, 13.
(19) Ilhan, M.; Long, J. P. *Arch. Int. Pharmacodyn. Ther.* 1975, *216*, 4.
(20) Ilhan, M.; Long, J. P.; Cannon, J. G. *Arch. Int. Pharmacodyn. Ther.* 1976, *222*, 70.
(21) Sharabi, F. M.; Long, J. P.; Cannon, J. G.; Hatheway, G. J. *J. Pharmacol. Exp. Ther.* 1976, *199*, 630.
(22) Cannon, J. G.; Hatheway, G. J.; Long, J. P.; Sharabi, F. M. *J. Med. Chem.* 1976, *19*, 987.
(23) Sharabi, F. M.; Long, J. P.; Cannon, J. G. *J. Pharmacol. Exp. Ther.* 1977, *202*, 97.

Table II. Cardiovascular Effects of Lergotrile (1), Pergolide (2), and 4-[2-Di-*n*-(Propylamino)ethyl]indole (9) in the Anesthetized Cat

		effect on mean arterial blood pressure		
no.	dose, μg/kg	% increase from resting control[a]	% decrease from resting control	% decrease in heart rate
1	30		22 ± 4	11 ± 3
	100		34 ± 5 (97 ± 7)[b]	10 ± 4 (152 ± 8)
	300		38 ± 6	12 ± 4
2	3	5 ± 2	5 ± 2	23 ± 3
	10	15 ± 4	8 ± 2 (110 ± 12)	59 ± 6
	30	52 ± 17	6 ± 2	80 ± 5
9	30	6 ± 2	11 ± 4	7 ± 2
	100	16 ± 2	18 ± 5 (101 ± 4)	12 ± 2 (123 ± 13)
	300	41 ± 21	10 ± 4	10 ± 4

[a] The primary pressor effect induced by pergolide (2) and 9 was transient and of short duration. [b] Values within parentheses indicate resting mean arterial blood pressure (mmHg) and resting heart rate (beats/min).

this respect. All compounds lowered mean arterial pressure and resting heart rate. Compound 9 did not antagonize the positive chronotropic responses to epinephrine or isoproterenol, nor did 9 antagonize the vasopressor response to epinephrine. Haloperidol (100 μg/kg) antagonized significantly the inhibition of the cardioaccelerator nerve preparation induced by 1, 2, and 9. In most preparations, the heart-rate reductions and inhibition of neural stimulation induced by 1 and 2 lasted 60 min. Comparable doses of 9 lasted 2–3 h or more.

In rats, 9 induced decreased locomotion during the 24-min period that was measured 6 min after sc administration. The ED_{50} (μmol/kg) and 95% confidence limits are 2.0 (0.33–4.1).

Following iv injection into cats, all compounds studied produced lowering of mean blood pressure, decrease in heart rate (Table II), and inhibition of positive chronotropic responses induced by stimulation of postganglionic fibers of the cardioaccelerator nerves. Compounds 1 and 9 required 30–40 min following iv administration to reach maximal inhibition of neural transmission. This slow rate of onset of action may indicate metabolic activation. The duration of effect of 9 was considerably greater than for 1 and 2. The inhibition by 9 of sympathetic neural transmission to the hearts, as well as the production of bradycardia, was not related to inhibition of β_1 receptors in the heart. The positive chronotropic responses induced by epinephrine or isoproterenol were not inhibited by 9. Likewise, 9 did not antagonize the vasopressor responses to epinephrine, indicating no inhibition of α_1 adrenoceptors of the arterial bed. Haloperidol (100 μg/kg) reversed neural inhibition produced by all compounds, which is evidence that they interact with dopaminergic inhibitory receptors on the adrenergic nerve terminal of cats.

Compound 9 induced decreased locomotion in rats. Whether this reflects synaptic dopaminergic neuronal inhibition in the striatum, or some other mechanism, has not been determined. However, this demonstrates the activity of 9 in a second animal species and indicates that it apparently crosses the blood–brain barrier.

None of the compounds produced renal vasodilatation, in accord with the report of McNay et al.[24] that lergotrile (1) does not dilate the renal vascular bed.

The biological data presented in this communication suggest that 9 (R = R′ = *n*-C_3H_7) is a dopaminergic agonist. In the anesthetized cat, lergotrile (1) and 9 are quite parallel in their actions and potencies. The data are consistent with the proposal that the structure of 9 is the active pharmacophore in the lergotrile and pergolide molecules. Bach et al.[11] have proposed that the dopaminergic pharmacophore of ergoline is the pyrroleethylamine moiety. This contrast remains to be clarified by further studies.

Acknowledgment. This work was supported by Grant GM-22365 from the National Institute of General Medical Sciences. Thanks are extended to Dr. E. C. Kornfeld and Eli Lilly & Co. for a generous gift of pergolide.

(24) McNay, J. L.; McDonald, R. H., Jr.; Goldberg, L. I. *Circ. Res.* 1965, *16*, 510.

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EXHIBIT I

79287-54-0; 7r, 79287-59-5; 7s, 79287-34-6; 7t, 79290-47-4; 7u, 101712-51-0; 7v, 101712-52-1; 7w, 101712-53-2; 7x, 101712-54-3; 7y, 101712-55-4; 7z, 101712-56-5; 7aa, 101712-57-6; 7bb, 101712-58-7; 7cc, 101712-59-8; 7dd, 101712-60-1; 7ee, 79287-60-8; 7ff, 79290-50-9; 7gg, 101712-61-2; 7hh, 79290-49-6; 7ii, 101712-62-3; 7jj, 101712-63-4; 7kk, 101712-64-5; 7ll, 79290-48-5; . (X = H), 90-43-7; 9 (X = 4-Cl), 64151-76-6; 10 (X = 4-Cl), 79287-41-5; 10 (X = H), 36697-38-6; 11 (X = 4-Cl), 79287-36-8; 11 (X = H), 19434-42-5; 12 (X = 4-OCH_3), 122-84-9; 12 (X = 2-OCH_3), 5211-62-1; 12 (X = 2,5-$(OCH_3)_2$), 14293-24-4; 12 (X = 3,4-$(OCH_3)_2$), 776-99-8; 12 (X = 4-CH_3), 2096-86-8; 12a (X = 4-Cl), 5586-88-9; 12a (X = 3-Cl), 14123-60-5; 12a (X = 2-Cl), 6305-95-9; 12b, 6097-32-1; 12c (X = 2-CF_3), 21235-67-6; 12c (X = 4-CF_3), 713-45-1; 12c (X = 3-CF_3), 21906-39-8; 12d, 770-39-8; 12e, 101712-18-8; 12f, 33744-50-2; 12g, 6304-16-1; 12h, 6302-03-0; 12i, 6302-02-9; 12j, 459-03-0; 12k, 1737-19-5; 12l, 2836-82-0; 12m, 101712-19-0; 12n, 101712-20-3; 12o, 19225-86-6; 12p, 88356-92-7; 13 (X = H, amine), 19434-42-5; 13a, 85841-96-9; 13a (amine), 79287-36-8; 13b, 79287-43-7; 13c, 79287-42-6; 13d, 79287-45-9; 13e, 79287-46-0; 13f, 79287-44-8; 13g, 79287-48-2; 13h, 63801-89-8; 13i, 23837-81-2; 13j, 101712-24-7; 13k, 31965-41-0; 13l, 101712-25-8; 13m, 101712-26-9; 13n, 101759-44-8; 13o, 101712-27-0; 13p, 69571-26-2; 13q, 33400-82-7; 13r, 79287-47-1; 13s, 101712-28-1; 13t, 101712-29-2; 13u, 101712-30-5; 13v, 101712-31-6; 13w, 101712-32-7; 13x, 101759-45-9; 4-$ClC_6H_4C_6H_4OCH_2$-2, 53824-23-0; 2-$IC_6H_4OCH_3$, 529-28-2; 4-ClC_6H_4I, 637-87-6; 4-$FC_6H_4CH_2CO_2H$, 405-50-5; 2-$F_3CC_6H_4CH_2CO_2H$, 3038-48-0; (*E*)-2-$F_3CC_6H_4CH$=C(OCOCH$_3$)CH_3, 101712-21-4; (*Z*)-2-$F_3CC_6H_4CH$=C(COCH$_3$)CH_3, 101712-22-5; C_6F_5CHO, 653-37-2; $O_2NCH_2CH_3$, 79-24-3; C_6F_5CH=C(NO$_2$)CH_3, 101712-23-8; $CH_3O(CH_2)_3OCHCl_2$, 3970-21-6; modisquine, 86-42-0; modisquine *N*-oxide, 1245-23-7; cycloquine, 14594-33-3; cycloquine *N*-oxide, 101712-96-3; 4-methylpyridine, 108-89-4; sodium nitromalonaldehyde, 34461-00-2; 4,7-dichloroquinoline, 86-98-6; 4,7-dichloroquinoline *N*-oxide, 1077-74-3.

Syntheses and in Vitro Evaluation of 4-(2-Aminoethyl)-2(3*H*)-indolones and Related Compounds as Peripheral Prejunctional Dopamine Receptor Agonists

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A series of (β-aminoethyl)indolones and related compounds was synthesized and evaluated in vitro as peripheral prejunctional dopaminergic agonists in the field-stimulated isolated perfused rabbit ear artery. 4-[2-(Di-*n*-propylamino)ethyl]-7-hydroxy-2(3*H*)-indolone (26) was the most potent compound (ED_{50} = 2 ± 0.3 nM) tested, while the related secondary amine 24 and the des-OH derivatives 28 and 34 were only slightly less potent. 4-Methoxybenzeneethanamine and 2-methyl-3-nitrophenylacetic acid were employed as starting materials for the synthesis of the 4-(β-aminoethyl)indolones. The ring-opened 3-acylamino analogues 46 and 47 were prepared via nitration of the phenethylamine 43 derived from 4-methoxyphenylacetic acid. The inactive isomeric indolones 38, 39, and 41 were derived from 4-nitrobenzeneethanamine and from indolone-6-acetic acid (13).

During the past decade, evidence has accumulated to show that there are two distinct dopamine receptors in peripheral tissues. The peripheral postjunctional (D_1) receptor, located primarily in specific vascular beds such as the renal, mesenteric, and coronary arteries, mediates vasodilation.[2] The existence of this receptor was first suggested by in vivo studies showing dopamine-induced increases in renal blood flow in the dog.[2] This vascular D_1 receptor closely resembles the adenylate cyclase linked dopamine receptor found in the central nervous system.[3]

Recently, Langer discovered that activation of a dopaminergic receptor located on sympathetic nerve terminals in the perfused cat spleen would inhibit the release of neurotransmitter evoked by nerve stimulation.[4] Subsequent studies have shown this prejunctional receptor to be present on terminals of many, but not all, sympathetic nerves, and although activation of this dopamine receptor has similar effects to activation of prejunctional α_2-adrenoceptors, these two neuroinhibitory receptors are pharmacologically distinct.[5] The peripheral prejunctional dopamine receptor, designated D_2 by most investigators, is sensitive to dopamine and apomorphine at nanomolar concentrations and appears not to be coupled to adenylate cyclase. Much higher concentrations of dopamine, in the micromolar range, are required to activate D_1 receptors, and apomorphine acts as a weak partial agonist.[4] In addition, D_1 and D_2 receptors can be differentiated with selective antagonists. The *l* enantiomer of sulpiride preferentially blocks the D_2 receptor, and the recently discovered benzazepine derivatives SCH23390[6] and SK&F 83566[7] are highly selective for the D_1 subtype.

Stimulation of peripheral D_2 receptors is likely to be of therapeutic benefit in the treatment of cardiovascular disorders characterized by inappropriately high sympathetic tone. By inhibition of neurotransmitter release from the cardiac sympathetic nerve terminals, a D_2 agonist should attenuate the increase in cardiac work induced by exercise, stress, or any other stimulus that results in increased sympathetic drive. An additional benefit would be expected from concurrent inhibition of transmitter release from vascular sympathetic terminals, which would limit increases in vascular resistance and lower cardiac afterload. These sympathoinhibitory actions should be proportional to the degree of sympathetic activation; therefore a peripheral D_2 agonist should have little effect during intervals of low stress when sympathetic drive is low.

[†]Department of Pharmacology.

(1) Brodde, O. E. *Life Sci.* 1982, *31*, 283–306.
(2) Goldberg, L. I.; Sommerville, P. F.; McNay, J. L. *J. Pharmacol. Exp. Ther.* 1958, *163*, 188–197.
(3) Kebabian, J. W.; Calne, D. B. *Nature (London)* 1979, *277*, 93–96.
(4) Langer, S. Z. *Biochem. Pharmacol.* 1974, *23*, 1793–1800.
(5) Dubocovich, M. L.; Langer, S. Z. *J. Pharmacol. Exp. Ther.* 1980, *212*, 144–152.
(6) Hilditch, A.; Drew, G. M.; Naylor, R. M. *Eur. J. Pharmacol.* 1984, *97*, 333–334.
(7) Berkowitz, B. A.; Zabko-Potapovich, B.; Sherman, S.; Hibble, J. P.; Weinstock, J.; Ohlstein, E. H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1984, *43*, 743.

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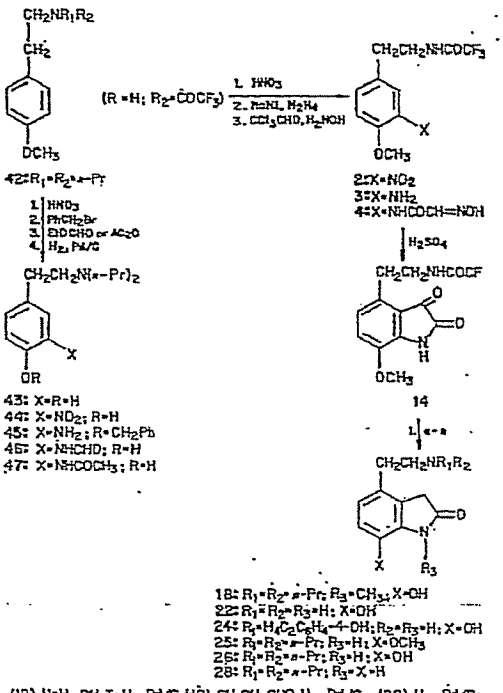
A number of different chemical structures have demonstrated preferential agonist activity at peripheral prejunctional D_2 vis-à-vis postjunctional D_1 receptors. These include for example alkylated derivatives of dopamine such as di-*n*-propyldopamine and *n*-propyl-*n*-butyldopamine; cyclized dopamine derivatives of the 2-aminotetralin series and apomorphine; ergot alkaloids such as bromocryptine and its simplified derivatives like LY141865.[7] Our work in the area of dopamine agonists has for a number of years been centered on chemistry within a series of catechol-containing 3-benzazepines. This has resulted in the discovery of agonists that act at both peripheral pre- and postjunctional dopaminergic sites,[9] as well as agents that act more selectively at postjunctional sites.[10] Our interest in dopaminergic agonists has more recently focused on the identification of a selective peripheral D_2 agonist that is not a catechol and that also does not contain the basic chemical framework of the ergots or ergolines. We believed that a potent and selective peripheral D_2 agonist free of the limiting side effects related to the presence of an ergot structure or catechol would be a useful sympatholytic drug for cardiovascular therapy.

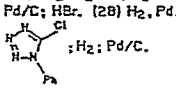
Our interest in the indolones was stimulated by the well-recognized prejunctional D_2 receptor agonist activity of certain ergot and ergoline derivatives including bromocriptine, lysergic acid diethylamide (LSD), lisuride, pergolide, and lergotrile.[8,11] We postulated, as others have done,[12,13] that the indoleethanamine fragment of the ergoline ring system was primarily responsible for the presynaptic dopaminergic receptor agonist activity of these compounds. By analogy with the reported active metabolites of the ergoline agonists,[13-15] we speculated that oxidative metabolism of the less complex indoleethanamines might lead to indolones of the kind described in this paper. The active ergolines were attractive models since they offered clues to the discovery of simpler non-catechol structures that might exhibit high presynaptic D_2 receptor selectivity.

On the basis of this hypothesis, we have synthesized and evaluated for sympatholytic activity a series of 4-(2-aminoethyl)indolones. We have recently communicated the syntheses and prejunctional dopaminergic activity of two of these compounds.[16,17] This paper describes in greater detail the syntheses of these agents and the preparation of a series of analogues related to them. All of the

Scheme I

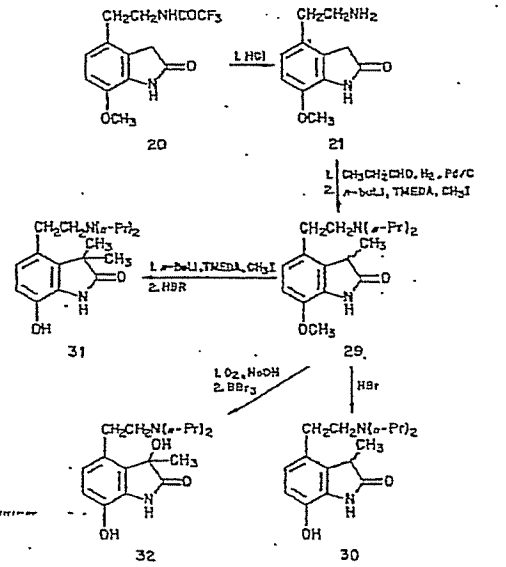


(18) NaH, CH_3I; H_2, Pd/C; HCl, CH_3CH_2CHO, H_2, Pd/C. (22) H_2, Pd/C; HBr. (24) H_2, Pd/C; HCl; $MeOPhCH_2CHO$; $NaBH_3CN$; HBr. (25) H_2, Pd/C; HCl; CH_3CH_2CHO, H_2 Pd/C. (26) H_2, Pd/C; HCl; CH_3CH_2CHO; H_2, Pd/C; HBr. (28) H_2, Pd/C; HCl; CH_3CH_2CHO, Pd/C; HBr;



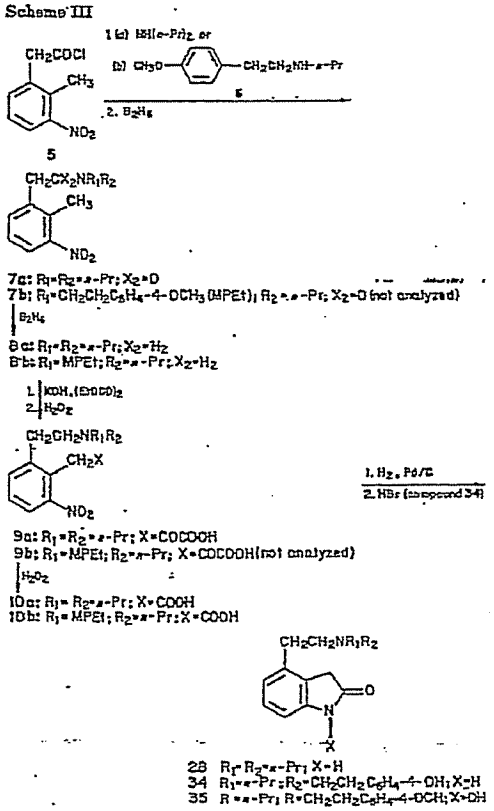
; H_2; Pd/C.

Scheme II

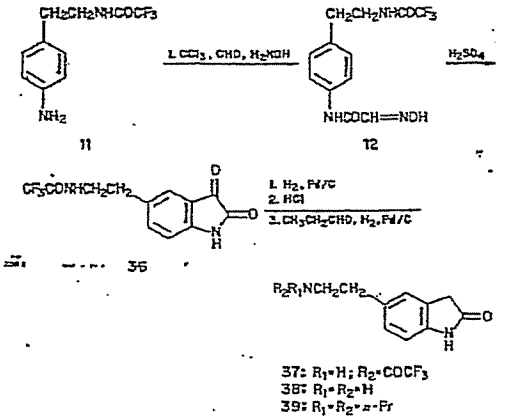


(8) For a comprehensive review of this area, see: Kaiser, C.; Jain, T. *Med. Res. Rev.* 1985, *5*, 145 and references therein.
(9) Blumberg, A. L.; Hieble, J. P.; McCafferty, J.; Hahn, R. A.; Smith, J., Jr. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1982, *41*, 1345 (Abstr).
(10) Weinstock, J.; Wilson, J. W.; Ladd, D. L.; Brush, C. K.; Pfeiffer, F. R.; Kuo, G. Y.; Holden, K. G.; Yim, N. C. F.; Hahn, R. A.; Wardell, J. R., Jr.; Tobia, A. J.; Setler, P. E.; Sarau, H. M.; Ridley, P. T. *J. Med. Chem.* 1980, *23*, 973–5.
(11) Kornfeld, E. C.; Bach, N. J.; Titus, R. D.; Nichols, C. L.; Clemens, J. A. *Acta Pharm. Suec.* 1983, Suppl. 2, 85–97. *Proceedings of the Symposium on Dopamine Agonists, Structure–Activity Relationships, Clinical Aspects*; Carlsson, E. A., Nilsson, J. L. G., Eds.; Sweden Pharm. Press: Stockholm, 1983; Vol. 2.
(12) Cannon, J. G. *Biosc.* 1979, *20*, 87–94.
(13) Cannon, J. G.; Lee, T.; Ilhan, M.; Kouns, J.; Long, J. P. *J. Med. Chem.* 1984, *27*, 386–389.
(14) Parli, J. C.; Schmidt, B.; Shear, C. *J. Biochem. Pharmacol.* 1978, *27*, 1405–1408.
(15) Siddik, Z. H.; Barnes, R. D.; Dring, L. G.; Smith, R. L.; Williams, R. T. *Biochem. Pharmacol.* 1979, *28*, 3093–3101.
(16) Huffman, W. F.; Hall, R. F.; Grant, J. A.; Wilson, J. W.; Hieble, J. P.; Hahn, R. A. *J. Med. Chem.* 1983, *26*, 933–935.
(17) Gallagher, G., Jr.; Lavanchy, P. G.; DeMarinis, R. M.; Wilson, J. W.; Hieble, J. P. *J. Med. Chem.* 1985, *28*, 1533–1538.

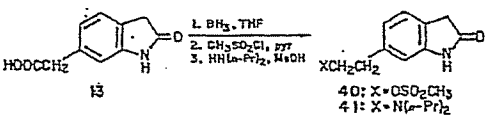
Scheme III



Scheme IV



Scheme V



final targets (Table IV) have been evaluated in vitro for their ability to stimulate peripheral prejunctional dopaminergic receptors by using as a screening procedure measurement of the inhibition of electrically stimulated neurotransmission in the isolated perfused rabbit ear artery.[18]

Chemistry. With the exception of 33–35, the 4-(aminoethyl)indoles included in Table I were derived from commercially available 4-methoxybenzeneethanamine as outlined in Schemes I and II. Compounds 33–35 were prepared from 2-methyl-3-nitrophenylacetic acid as shown in Scheme III. Compound 28 was prepared via Scheme III but was also obtained by hydrogenolysis of the phenyltetrazole ether 27 (Table I). The isomeric indolones 37–39 (Table II) were obtained from *N*-[2-(4-aminophenyl)ethyl]-2,2,2-trifluoroacetamide (11) by utilizing the Sandmeyer isatin synthesis (Scheme IV), and 6-[2-(di-*n*-propylamino)ethyl]indolone (41) was elaborated as outlined in Scheme V, from the known indolone-6-acetic acid (13). The ring-opened 3-acylamino analogues 46 and 47 (Table III) were prepared from commercially available 4-methoxyphenylacetic acid by using the procedures outlined in Scheme I.

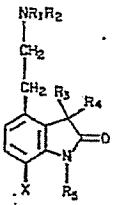
Biological Results

Compounds 22, 26, and 28 (Tables I and IV) are potent inhibitors of the constrictor response of the perfused rabbit ear artery (REA) to electrical field stimulation, and this effect is competitively antagonized by the dopaminergic receptor antagonist (*S*)-sulpiride. Our data show that the pharmacological effects of 26 and 28 are mediated primarily through activation of peripheral prejunctional D_2 receptors, since neither 26 nor 28 is able to stimulate or block the dopamine-sensitive adenylate cyclase of rat caudate at concentrations up to 10^{-4} M and neither causes the stimulation of motor activity in rats at doses up to 1 mg/kg iv.[19–23] On the other hand, compound 22 does stimulate the cyclase significantly at 10^{-4} M, and this may be indicative of an ability, albeit weak, to activate postjunctional D_1 receptors. We believe that the potency of 26 in the REA assay coupled with its the lack of effects associated with activation of postjunctional D_2 receptors is additional evidence of significant differences in peripheral pre- and postjunctional receptors.

Comparison of the in vitro potency of 22 and 26 with the catechol standards DA and *N,N*-di-*n*-propyldopamine (DPDA) suggests equivalency of the lactam unit and the 3-OH of DA and DPDA in terms of receptor recognition. Such a hypothesis is supported in part by the significant in vitro activity observed with the des-OH compounds 28 and 34 (Tables I and IV) and the loss of activity observed with the isomeric indolones 38, 39, and 41 (Tables II and IV). It is of interest that the des-OH indolones 28 and 34 show in vitro potencies in the REA assay in the range of DA and DPDA, since the phenolic derivative *N,N*-di-*n*-

(18) Steinsland, O. S.; Hieble, J. P. *Science* 1978, *199*, 443–445.
(19) Sulpizio, A. C.; Fowler, P. J.; Hieble, J. P.; Gallagher, G.; Wilson, J. W.; DeMarinis, R. M. *Pharmacologist* 1984, *26*, 174 (Abstr).
(20) Zeld, R. L.; Hieble, J. P.; DeMarinis, R. M.; Wilson, J. W. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1984, *43*, 1020 (Abstr).
(21) Hieble, J. P.; Jarvay, C. A.; Gruber, F. H.; Serau, H. M.; Foley, J. J.; Wilson, J. W.; DeMarinis, R. M. *Pharmacologist* 1983, *25*, 162 (Abstr).
(22) Detailed biological characterization of compounds 25 and 28 will be reported in forthcoming manuscripts.
(23) Summers, C.; Dijkstra, D.; deVries, J. B.; Horn, A. S. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1981, *316*, 304–310.

Table I. 4-(2-Aminoethyl)indolones and Intermediates



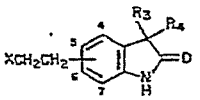
compd	R_1	R_2	R_3	R_4	R_5	X	formula[a]	scheme/ method[b]	mp, °C	solvent	yield, %
14	H	$COCF_3$	$R_3, R_4 = O$		H	OCH_3	$C_{22}H_{21}F_3N_2O_4$	I	236.5–238	EtOAc–hexane	64
15	H	$COCF_3$	$R_3, R_4 = O$		CH_3	OCH_3	$C_{21}H_{19}F_3N_2O_4$	I	203–205	EtOH	64
16	H	$COCF_3$	H	H	CH_3	OCH_3	$C_{21}H_{21}F_3N_2O_3$	I/A	185–187	EtOH–H_2O	46
17	H	H	H	H	CH_3	OCH_3	$C_{19}H_{20}N_2O_2$·HCl	I	235–237	EtOH	76
18	*n*-Pr	*n*-Pr	H	H	CH_3	OH	$C_{17}H_{26}N_2O_2$·HBr·0.25H_2O	I/B, C	227–229	H_2O	57
19	H	$COCF_3$	$R_3, R_4 = -SCH_2CH_2S-$		H	OCH_3	$C_{23}H_{23}F_3N_2O_3S_2$	I	163.5	EtOAc–hexane	85
20	H	$COCF_3$	H	H	H	OCH_3	$C_{22}H_{21}F_3N_2O_3$·0.5H_2O	I/A[c]	178–179	EtOAc–CH_2Cl_2	73
21	H	H	H	H	H	OCH_3	$C_{11}H_{14}N_2O_2$·HCl·0.5H_2O	I	258–260.5	MeOH–EtOAc	91
22	H	H	H	H	H	OH	$C_{10}H_{12}N_2O_2$·HBr	I/C	250 dec	48% HBr (H_2O)	83
23	H	H_4C_2–C_6H_4–4–OCH_3	H	H	H	OCH_3	$C_{20}H_{24}N_2O_3$·HCl	I	258–260 dec	CH_3CN	22
24	H	H_4C_2–C_6H_4–4–OH	H	H	H	OH	$C_{18}H_{20}N_2O_3$·HBr	I/C	313–315 dec	48% HBr (H_2O)	87
25	*n*-Pr	*n*-Pr	H	H	H	OCH_3	$C_{17}H_{26}N_2O_2$·HCl	I/B	231–234	CH_3CN	72
26	*n*-Pr	*n*-Pr	H	H	H	OH	$C_{16}H_{24}N_2O_2$·HBr	I/C	252–254	MeOH–EtOAc	75
							$C_{16}H_{24}N_2O_2$·HCl		278–283	H_2O	
27	*n*-Pr	*n*-Pr	H	H	H		$C_{25}H_{32}N_4O_2$·HCl	I	245–246	CH_3CN	86
28	*n*-Pr	*n*-Pr	H	H	H	H	$C_{15}H_{22}N_2O$·HCl	I, III	241–243	CH_3CN	76, 78[e]
29	*n*-Pr	*n*-Pr	H	CH_3	H	OCH_3	$C_{18}H_{28}N_2O_2$·HCl	II	195–196	CH_3CN	68
30	*n*-Pr	*n*-Pr	H	CH_3	H	OH	$C_{17}H_{26}N_2O_2$	II/C	183–185	EtOAc	69
31	*n*-Pr	*n*-Pr	CH_3	CH_3	H	OH	$C_{18}H_{28}N_2O_2$·HBr	II/C	210–212	CH_3CN	24
32	*n*-Pr	*n*-Pr	CH_3	OH	H	OH	$C_{17}H_{26}N_2O_3$ (0.4 M NaCl)	II	~120 dec	EtOAc–Et_2O	5
33	*n*-Pr	H_4C_2–C_6H_4–4–OCH_3	H	H	H	H	$C_{22}H_{28}N_2O_2$·HCl	III	156–158	CH_3CN	22
34	*n*-Pr	H_4C_2–C_6H_4–4–OH	H	H	H	H	$C_{21}H_{26}N_2O_2$·HBr·0.5H_2O	III/C	175 dec	CH_3CN	74
35	*n*-Pr	H_4C_2–C_6H_4–4–OCH_3	H	H	OH	H	$C_{22}H_{28}N_2O_4$·HCl	III	196–197.5	CH_3CN	31

[a] All compounds analyzed satisfactorily for C, H, and N unless indicated otherwise. [b] For methods A–C, see Experimental Section. I indicates that the procedure is described in the Experimental Section. [c] Preferably prepared directly from 14 by method A (71%). [d] Elemental analytical data was not obtained for this document. [e] This compound was prepared via Scheme I (78%) and Scheme III (78%).

propyl-*m*-tyramine (DPMT), which has been reported to have in vivo central nervous system effects[23] but no activity in an in vitro assay for peripheral dopaminergic activity,[24] is also 1 order of magnitude less active in our REA assay then the nonphenolic indolones 28 and 34. Comparison of the assay results for compound 26 with those obtained for the ring-opened analogues 45 and 47 (Table III and IV) in the REA demonstrates a unique potency associated with the lactam ring of 26.

(24) Schmidt, M.; Imbs, J. L.; Giesen, E. M.; Schwartz, J. *Eur. J. Pharmacol.* 1982, *84*, 61–70.

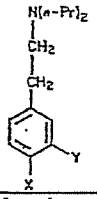
Table II. Isomeric (2-Aminoethyl)indolones and Intermediates



no.	R^3, R^4	side-chain posit	X	formula[a]	scheme/method[b]	mp, °C	solvent	yield, %
36	O	5	$NHCOCF_3$	$C_{12}H_8F_3N_2O_2$	IV	194–194.5	EtOAc	82
37	H	5	$NHCOCF_3$	$C_{12}H_{11}F_3N_2O_2$	IV/A	203–204	AcOH–H_2O	83
38	H	5	NH_2	$C_{10}H_{12}N_2O$·HCl	IV	276–280	MeOH	77
39	H	5	$N(n\text{-}Pr)_2$	$C_{16}H_{24}N_2O$·HCl	IV/B	185.5–186.5	EtOH–Et_2O	70
40	H	6	OSO_2CH_3	$C_{11}H_{13}NO_4S$	V	155.5–158	CH_2Cl_2	78
41	H	6	$N(n\text{-}Pr)_2$	$C_{16}H_{24}N_2O$·HCl·H_2O[c]	(phase change) 108	ppt from Et_2O	85	

[a] See footnote a, Table I. [b] See footnote b, Table I. [c] N: calcd, 8.90; found, 8.47.

Table III. Ring Opened Analogues



compd	X	Y	formula	scheme/method[a]	mp, °C	solvent	anal.	yield, %
42	OCH_3	H	$C_{12}H_{17}NO$	I	bp 113–116 °C (0.5 torr)		C,[b] H, N	75
43	OH	H	$C_{11}H_{15}NO$·HBr	I/C	154–155	MeOH–Et_2O	C, H, N	88
44	OH	NO_2	$C_{11}H_{14}N_2O_3$	I	60.5–61.5	EtOH–H_2O	C, H, N	48
45	OCH_2Ph	NH_2	$C_{23}H_{26}N_2O$·2HCl·$2H_2O$	I	107–110 dec	2-PrOH–Et_2O	C, H, N	71
46	OH	NHCHO	$C_{12}H_{16}N_2O_2$·HCl·$2H_2O$	I	241.5–216.5	MeOH–Et_2O	C, H,[c] N	63
47	OH	$NHCOCH_3$	$C_{13}N_{18}N_2O_2$·HCl	I	164.5–165.5	MeOH–Et_2O	C, H, N	85

[a] See footnote b, Table I. [b] C: calcd, 76.55; found, 75.70. [c] H: calcd, 8.68; found, 8.05.

Table IV. Agonist Activity of 4-(Aminoethyl)indolones and Related Compounds at the Prejunctional Dopamine Receptor

compd	EC_{50},[a] nM	N[b]	compd	EC_{50},[a] nM	N[b]
18	>3000	4	34	28 ± 19	9
22	116 ± 43[c]	8	38	>3000	2
24	53 ± 16	6	39	3000	2
25	>3000	2	41	>3000	2
26	2 ± 0.3[c]	10	45	750 ± 188	5
28	100 ± 26[c]	5	47	>10000	6
30	18 ± 3	11	DA[d]	73 ± 5[e]	38
31	>3000	2	DPDA[d,e]	80 ± 17[e]	13
32	218 ± 26	5	DPMT[d,f]	700 ± 209	5

[a] Concentration SE required to inhibit by 50% the vasoconstrictor response to field stimulation in the isolated, perfused rabbit ear artery. See: Hieble, J. P.; Pendleton, R. G. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *309*, 217. [b] Number of determinations. [c] This response competitively antagonized by (*S*)-sulpiride. [d] DA = dopamine, DPDA = *N,N*-di-*n*-propyldopamine, DPMT = *N,N*-di-*n*-propyl-*m*-tyramine. [e] Cannon, J. G.; Hsu, F. L.; Long, J. P.; Flynn, J. R.; Costell, B.; Naylor, R. J. *J. Med. Chem.* **1978**, *21*, 248. [f] Wikström, H.; Lindberg, P.; Martinson, P.; Hjorth, S.; Carlsson, A.; Hacksell, U.; Svensson, U.; Nilsson, J. L. G. *J. Med. Chem.* **1978**, *21*, 864.

Starting from what we believed to be the intrinsic pharmacophore of the ergots, coupled with the knowledge of the presynaptic selectivity of alkylated dopamine analogues vis-à-vis dopamine itself, we have designed and synthesized a series of indolones of which several possess potent presynaptic dopaminergic agonist activity as their major pharmacological property. These compounds do not possess the complex ergot ring structure and do not contain the catechol moiety. Preliminary studies on the in vivo characterization of two of the most interesting congeners, 26 and 28, have been reported[16,17] and more detailed pharmacological characterization of these compounds will be published in future papers.

Experimental Section

Melting points were taken either in a Mel-Temp hot stage or in open capillary tubes with a Thomas-Hoover Unimelt apparatus and are uncorrected. When analyses are reported by symbols of the elements, results were within 0.4% of calculated values. Melting points, and yields are recorded for new compounds in Schemes I–II. IR spectra were recorded on a Perkin-Elmer Model 683 spectrophotometer and ^{1}NMR spectra were obtained on a Varian EM-390 spectrometer. Spectral data for all compounds were consistent with assigned structures. The C, H, and N analyses were carried out by the Analytical, Physical and Structural Chemistry Department of Smith Kline & French Laboratories.

N-[2-(4-Methoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (1). To a cold solution of 50.0 g (0.331 mol) of 4-methoxybenzeneethanamine in 500 mL of CH_2Cl_2 under an argon atmosphere was added dropwise with stirring a solution of 93.6 mL (0.664 mol) of $(CF_3CO)_2O$ in 60 mL of CH_2Cl_2. After the mixture was stirred at room temperature for 1.5 h, the volatiles were removed, toluene was added and removed, and the residue was crystallized from 800 mL of 1:1 Et_2O–petroleum ether to give 55.8 (68.2%) of white needles of 1, mp 84.0 °C. An additional 16.6 g, mp 82.5–84.0 °C, was recovered from the filtrate to give a total yield of 72.4 g (88.4%). Anal. ($C_{11}H_{12}F_3NO_2$) C, H, N.

N-[2-(4-Methoxy-3-nitrophenyl)ethyl]-2,2,2-trifluoroacetamide (2). To a solution of 30.0 g (0.121 mol) of 1 in 254 mL of TFA under an argon atmosphere was added dropwise with stirring and cooling a solution of 7.5 mL (0.12 mol) of concentrated HNO_3 in 56 mL of TFA. After the mixture was stirred at room temperature for 2 h, the solvents were removed and the residue was dissolved in EtOAc, which was successively extracted with 5% HCl, dilute $NaHCO_3$, and brine and then dried ($MgSO_4$, activated carbon). The mixture was filtered and the filtrate

concentrated. The resulting crude amber solid, 34.8 g (98%), was crystallized from 400 mL of 1:3 EtOAc–hexane to give 25.3 g (71.5%) of **2**, mp 92.5–93.0 °C. A second crop, 4.59 g (13%), mp 90–92 °C, of **2** was obtained from the mother liquors. Anal. ($C_{11}H_{11}F_3N_2O_4$) C, H, N.

***N*-[2-(3-Amino-4-methoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (3).** To a mixture of 80 g of activated Raney nickel catalyst and a solution of 400 g (1.369 mol) of **2** in 4 L of EtOH was added dropwise with cooling and stirring under an argon atmosphere a solution of 200 mL (4.115 mol) of hydrazine hydrate in 2 L of EtOH. Stirring was continued at 15 °C for 2 h and 92 mL of HOAc was added dropwise to bring the pH to 7.0. The mixture was filtered and the filtrate treated with activated carbon. The carbon was removed, and the volatile solvents were evaporated in vacuo. The semisolid residue was triturated with EtOAc and the residual solid removed by filtration and washed with EtOAc. After extraction three times with brine, the EtOAc solution was dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in 1770 mL of Et_2O and 1000 mL of hexane was added. After cooling, 221.7 g of **3**, mp 87–88 °C was obtained. A second crop, 52.2 g (total yield 76.3%), was recovered from the filtrate. Anal. ($C_{11}H_{13}F_3N_2O_2$) C, H, N.

***N*-[2-[3-[(Hydroximinoacetyl)amino]-4-methoxyphenyl]-ethyl]-2,2,2-trifluoroacetamide (4).** A mixture of 44.5 g (0.17 mol) of **3**, 240 mL of H_2O, and 11.5 mL (0.207 mol) of concentrated H_2SO_4 was combined with a mixture of 29.1 g (0.176 mol) of chloral hydrate, 87.5 g (0.533 mol) of hydroxylamine sulfate, and 240 mL of H_2O. This mixture was heated rapidly to reflux in an argon atmosphere and after 4 min of reflux was allowed to cool to room temperature. The crude solid product was filtered, washed with H_2O, and dried. The residue was dissolved in hot EtOAc, clarified with activated carbon, and diluted at reflux with hexane. Upon cooling, 27.5 g (50%) of **4** mp 195–197 °C, was obtained. A second crop 9.9 g, mp 192–195 °C (total yield 68%), was obtained from the filtrate. ^1H NMR (Me_2SO-d_6/$CDCl_3$) δ 2.52–3.52 (m, 4 H, CH_2), 3.81 (s, 3 H, OCH_3), 6.82 (d, 2 H), 7.53 (s, 1 H), 8.18 (s, 1 H (exch)), 8.90 (s, 2 H (exch)), 11.90 (s, 1 H (exch)). Anal. ($C_{13}H_{14}F_3N_3O_4$) C, H, N.

7-Methoxy-4-[2-(trifluoroacetamido)ethyl]isatin (14). One portion, 5.0 g (0.015 mol), of powdered **4** was added with stirring to 50 mL of concentrated H_2SO_4 under argon at 80 °C. Heating was continued for 6 min after solution was achieved. The reaction solution was poured over 500 g of cracked ice and the product was taken into EtOAc by two 200-mL extractions. The EtOAc solution was extracted with dilute aqueous $NaHCO_3$ and brine and then dried ($MgSO_4$). After removal of the $MgSO_4$, the solution was filtered through 200 g of silica gel and the filtrate evaporated to give 3.05 g of red crystalline **14**: IR (KBr) 1750, 1735, 1705 cm^{-1}; ^1H NMR (Me_2SO-d_6/$CDCl_3$) δ 3.08 (t, 2 H, CH_2), 3.50 (t, 2 H, CH_2), 3.90 (s, 3 H, OCH_3), 6.82 (d, 1 H, J = 9 Hz), 7.12 (d, J = 3 H, 1 H), 9.12 (m, 1 H (exch)).

7-Methoxy-1-methyl-4-[2-(trifluoroacetamido)ethyl]isatin (15). A mixture of 0.632 g (0.002 mol) of **14** and NaH, 0.058 g (0.0024 mol), in 10 mL of dry THF was treated with CH_3I, 1.14 g (0.008 mol), in three portions over a period of 2 days at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted into 95:5 EtOAc–EtOH and crystallized from EtOH after removal of solvent; 0.43 g of **15**: IR (Nujol) 1735, 1720, 1690 cm^{-1}; ^1H NMR ($MeOH$-d_4/$CDCl_3$) δ 3.11 (t, J = 6 Hz, 2 H, CH_2), 3.48 (t, J = 6 Hz, 2 H, CH_2), 3.59 (s, 3 H, NCH_3), 3.92 (s, 3 H, OCH_3), 6.85 (d, J = 9 Hz, 1 H (Ar), 7.17 (d, J = 9 Hz, 1 H (Ar).

7-Methoxy-1-methyl-4-[2-(trifluoroacetamido)ethyl]-2-(3*H*)-indolone (16). A mixture of 0.430 g (0.0013 mol) of **15** and 0.22 g of 10% Pd/C catalyst in 20 mL of HOAc containing 0.2 mL of 70% perchloric acid was hydrogenated at 50 °C for 8 h. After removal of the catalyst and solvent, H_2O and EtOAc were added to the residue, and the mixture was brought to pH 7 with NaOAc. The EtOAc phase was separated and the solvent removed in vacuo. Crystallization of the pink solid residue from 90:10 H_2O–EtOH gave 0.19 g of **16** as orange needles: IR (KBr) 1720, 1690 cm^{-1}; ^1H NMR ($MeOH$-d_4/$CDCl_3$) δ 2.75 (t, J = 6 Hz, 2 H, CH_2), 3.47 (s, 3 H, NCH_3), 3.51 (t, J = 5 Hz, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 6.81 (s, 2 H (Ar)).

This general procedure for the catalytic conversion of isatins to indolones has been used in the preparation of other compounds (Tables I and II) and is designated method A.

4-(2-Aminoethyl)-7-methoxy-1-methyl-2(3*H*)-indolone Hydrochloride (17). A solution of 0.41 g (0.0013 mol) of **16** in 2.5 mL of EtOH and 5.4 mL of H_2O containing 1.5 mL of concentrated HCl was refluxed for 20 h under a N_2 atmosphere. The solution was taken to dryness in vacuo. The residue was triturated with CH_3CN and Et_2O and crystallized from EtOH to yield 0.25 g.

4-[2-(Di-*n*-propylamino)ethyl]-7-hydroxy-1-methyl-2-(3*H*)-indolone Hydrobromide (18). A solution of 0.180 g (0.0007 mol) of **17** in 30 mL of HOAc containing 0.128 g (0.0022 mol) of propionaldehyde and 85 mg of 10% Pd/C catalyst was hydrogenated at 50 °C and 45 psi for 7 h. The catalyst and solvent were removed, and the residue was dissolved in H_2O and made alkaline with Na_2CO_3. The free base was extracted into EtOAc. The EtOAc was removed in vacuo and the residue was refluxed under nitrogen with 3 mL of 48% HBr for 4 h. After removal of the HBr in vacuo, the residue was crystallized from H_2O to give 0.15 g of rust colored crystals: IR (KBr) 1672 cm^{-1}; ^1H NMR (D_2O) δ 1.35 (t, 6 H, CCH_3), 2.10 (m, 4 H, CCH_2C), 3.05–3.64 (m, 9 H), 3.65 (s, 3 H, NCH_3), 7.19 (s, 2 H (Ar)).

The reductive alkylation procedure described in this experiment has been used for the preparation of other compounds (Tables I and II) and is designated method B. The ether cleavage procedure similarly has been used in other instances and is designated method C.

3,3-(Ethylenedithio)-7-methoxy-4-[2-(trifluoroacetamido)ethyl]-2(3*H*)-indolone (19). A mixture of 23.9 g (0.076 mol) of **14** and 28.0 mL (0.32 mol) of ethanedithiol in 700 mL of anhydrous CH_2Cl_2 was stirred at room temperature under argon while 6.3 mL (0.051 mol) of freshly distilled boron trifluoride etherate was added. After stirring at room temperature for 16 h, an additional 1.0 mL (0.008 mol) of boron trifluoride etherate was added and stirring was continued for 7 h. The mixture was diluted with 1500 mL of CCl_4 and cooled overnight at −23 °C. The solid was removed and dissolved in EtOAc/Et_2O, and this solution was extracted with H_2O, aqueous $NaHCO_3$, and brine. After drying ($MgSO_4$) and treatment with activated carbon, the solvent was removed and the residue recrystallized from EtOAc–hexane; 19.7 g (67%) of **19**. A second crop, 5.6 g (18%), was recovered from the filtrate.

7-Methoxy-4-[2-(trifluoroacetamido)ethyl]-2(3*H*)-indolone (20). To a partial solution of 1 g (0.0026 mol) of **19** in 10 mL of absolute EtOH under argon was added with stirring 8 g of Raney nickel catalyst in 50 mL of absolute EtOH. After the mixture was stirred for 2 h, the catalyst was removed and the solvent removed. The residue was dissolved in EtOAc and extracted with 3 N HCl, H_2O, 5% $NaHCO_3$, and brine. After drying ($MgSO_4$) and treatment with activated charcoal, the EtOAc was removed and the residue crystallized from EtOAc–hexane to yield 0.561 g (73%) of **20**, mp 176–178 °C. A solution in EtOAc–CH_2Cl_2 was filtered through silica gel to give 540 mg: mp 178–179 °C; IR (KBr) 1735, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (t, 2 H), 3.49 (s, 2 H, CH_2CO), 3.60 (t, 2 H), 3.85 (s, 3 H, OCH_3), 6.76 (s, 2 H (AR)), 7.56 (br s, 1 H (exch)).

4-(2-Aminoethyl)-7-methoxy-2(3*H*)-indolone (21). The amide **20**, 28.0 g (0.093 mol), was hydrolyzed as described for the preparation **17** to give 20.4 g of copper-colored needles.

4-[2-[[2-(*p*-Methoxyphenyl)ethyl]amino]ethyl]-7-methoxy-2(3*H*)-indolone Hydrochloride (23). 4-Methoxyphenylacetaldehyde was prepared by a modification of procedures described by Ban and Oishi[25] and by Hino and co-workers.[26] To a mixture of 5.0 g (0.0192 mol) of **21** and 0.88 g (0.016 mol) of KOH in 50 mL of MeOH was added with stirring 2.88 g (0.0192 mol) of the freshly distilled (bp 117–118 °C (9 mmHg)) 4-methoxyphenylacetaldehyde. To the resulting mixture was added 0.48 g (0.0078 mol) of sodium cyanoborohydride. After the mixture was stirred at room temperature for 3 days, an additional 1.0 g (0.0159 mol) of sodium cyanoborohydride was added and the pH was adjusted to 6.3. After the mixture was stirred an additional 4 h, H_2O was added and the pH adjusted to 12. The mixture was

(25) Ban, Y.; Oishi, T. *Chem. Pharm. Bull.* **1958**, *6*, 574–576.
(26) Hino, T.; Suzuki, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1973**, *21*, 2785–2789.

extracted three times with CH_2Cl_2. The solvents were removed in vacuo, and the residual oil was dissolved in Et_2O and made acidic by the addition of ethereal HCl. The solid salt that precipitated was triturated with EtOAc and crystallized from CH_3CN to give 1.6 g of 23.

4-[2-(Di-*n*-propylamino)ethyl]-7-methoxy-3(*R*,*S*)-methyl-2(3*H*)-indolone Hydrochloride (29). The procedure of Kende and Hodges[27] was employed. To a cold solution (−78 °C) of 2.18 g (0.0075 mol) of the free base of 25 in 50 mL of dry THF containing 2.3 mL (0.015 mol) of tetramethylethylenediamine under a nitrogen atmosphere were added 0.99 g (0.0155 mol) of cold *n*-butyllithium in hexane and then 2.13 g (0.015 mol) of CH_3I. After 1 h the temperature was allowed to rise slowly (3.5 h) to room temperature. The reaction mixture was poured into a saturated aqueous NH_4Cl solution and the product extracted into Et_2O. After drying ($MgSO_4$), ethereal HCl was added to the Et_2O solution and the orange oil that separated was triturated repeatedly with Et_2O. Recrystallization of the resulting granular solid from CH_3CN gave 1.74 g of 29: ^1H NMR (D_2O) δ 1.05 (t, 6 H, CH_3), 1.40 (d, 3 H, CH_3), 1.54–2.05 (m, 4 H), 2.70–3.60 (m, 10 H), 3.89 (s, 3 H, OCH_3), 6.92 (s, 2 H (Ar)).

3,3-Dimethyl-4-[2-(di-*n*-propylamino)ethyl]-7-hydroxy-2-(3*H*)-indolone Hydrobromide (31). The alkylation procedure employed for the preparation of 29 was repeated with use of 0.61 g (0.002 mol) of the free base of 29 as the starting material. The crude product consisted of a mixture of 29 and the 7-methoxy derivative of 31. An alkaline suspension (dilute NaOH) of the crude product was stirred at room temperature in the open air for 18 h. After cooling, the pH was adjusted to 9 with concentrated HCl and the crude product was extracted into Et_2O. The desired intermediate was separated from the oxidation product of 29 (the methyl ether of 32) by chromatography on Baker 40-μm silica gel with use of 1:1 aceton–petroleum ether. Without further purification, this material was converted to the desired product 31 with 2 mL of 48% HBr by using method C: ^1H NMR (D_2O) δ 1.05 (t, 6 H, CH_2CH_3), 1.44 (s, 6 H, $C(CH_3)_2$), 1.59–2.04 (m, 4 H), 2.95–3.52 (m, 8 H), 6.89 (s, 2 H (Ar)).

3,7-Dihydroxy-4-[2-(di-*n*-propylamino)ethyl]-3-methyl-2-(3*H*)-indolone (32). To a solution of 0.33 g (0.001 mol) of 29 in a mixture of 4 mL of MeOH and 5 mL of H_2O was added 0.5 mL of 40% NaOH. This reaction mixture was stirred in the open air at room temperature for 18 h and then diluted with ice, and the pH was adjusted to 2 with dilute HCl. After 30 min the pH was brought to 8.5 with dilute NaOH, and the aqueous phase was saturated with NaCl and extracted with EtOAc. The EtOAc extract was chromatographed on 40-μm Baker silica gel with 190:10:1 EtOAc–MeOH–concentrated NH_4OH to give 0.048 g of intermediate as the free base. A cold (−75 °C) solution of 0.064 g (0.0002 mol) of this intermediate in 5 mL of dry CH_2Cl_2 was treated with 1.1 mL of 1 M BBr_3 in CH_2Cl_2. The reaction was allowed to warm slowly to room temperature and was then stirred for 18 h. The solvent was removed in a stream of N_2. Ice containing 2 drops of concentrated NH_4OH was added to the residue. The pH was adjusted to 2 with 3 N HCl and after 15 min readjusted to 8 with use of 10% $NaHCO_3$. The aqueous phase was saturated with NaCl and exhaustively extracted with EtOAc. The EtOAc was removed in vacuo and the residual oil triturated with 1:1 Et_2O–petroleum ether to give 0.021 g of 32: ^1H NMR ($CDCl_3$) δ 1.05 (t, 6 H, CH_2CH_3), 1.58–2.02 (m, 4 H), 1.70 (s, 3 H, $HOCCH_3$), 3.00–3.50 (m, 8 H), 6.98 (s, 2 H (Ar)); IR (KBr) 1721 cm^{-1}.

4-[2-(Di-*n*-propylamino)ethyl]-7-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]-2(3*H*)-indolone Hydrochloride (27). A modification of the procedure of Teitel and O'Brien[28] was employed. A mixture of 3.43 g (0.0096 mol) of 25, 2.03 g (0.021 mol) of anhydrous K_2CO_3, and 1.77 g (0.099 mol) of 5-chloro-1-phenyl-1*H*-tetrazole in 220 mL of acetone, 60 mL of DMF, and 10 mL of H_2O was refluxed for 18 h. The mixture was filtered, and after the filtrate was concentrated in vacuo, the residue was diluted with H_2O, saturated with NaCl, and extracted with Et_2O. After drying ($MgSO_4$), the ether solution was treated with ethereal HCl. The solid residue was triturated with Et_2O and crystallized from CH_3CN to give 3.8 g of white crystalline product: ^1H NMR (MeOH-d_4) δ 1.08 (t, 6 H, CH_2CH_3), 1.61–2.09 (m, 4 H), CH_2CH_3), 2.95–3.57 (m, 10 H), 7.05 (d, 1 H (Ar)), 7.26 (d, 1 H (Ar), 7.53–7.97 (m, 5 H (Ar)); IR (KBr) 1738, 1710 cm^{-1}.

4-[2-(Di-*n*-propylamino)ethyl]-2(3*H*)-indolone Hydrochloride (28) (via Scheme I). A mixture of 2.64 g (0.00578 mol) of 27 and 1.49 g of 10% Pd/C catalyst in 200 mL of HOAc was hydrogenated for 20 h at 50 psi and 50 °C. The catalyst was removed and the solution concentrated in vacuo. The residue was partitioned between H_2O/EtOAc and acidified with dilute HCl. The aqueous phase was made alkaline (pH 8.5) with 10% NaOH. The product was extracted into EtOAc/Et_2O and after drying ($MgSO_4$), this solution was treated with ethereal HCl to give a pale yellow crystalline product: ^1H NMR ($CDCl_3$–MeOH-d_4) δ 1.05 (t, 6 H, CH_2CH_3), 1.58–2.08 (m, 4 H, CH_2CH_3), 2.98–3.50 (m, 10 H), 6.75–7.35 (m, 3 H (Ar)); IR (KBr) 1760, 1725, 1705 cm^{-1}.

2-(2-Methyl-3-nitrophenyl)-*N*,*N*-di-*n*-propylacetamide (7a). To 50.0 g (0.256 mol) of 2-methyl-3-nitrophenylacetic acid[29] was added dropwise with stirring 95 g (0.80 mol) of $SOCl_2$. When gas evolution ceased, the solution was concentrated in vacuo, and several small portions of dry toluene were added and removed in vacuo. The residue was dissolved in 300 mL of toluene and added at 10 °C to 600 mL of a 50:50 H_2O–toluene mixture containing 30 g (0.283 mol) of Na_2CO_3. Di-*n*-propylamine, 30.1 g (0.30 mol), was added with cooling and slow stirring, and after 0.5 h the mixture was brought to room temperature and stirred for an additional hour. An additional 1.0 g (0.0094 mol) of Na_2CO_3 was added and the toluene phase was separated, washed with 5% Na_2CO_3, 1.5 N HCl, and H_2O. After drying ($MgSO_4$), the solvent was removed and the thick residual oil was distilled in a Kugelrohr apparatus to give 64 g of product, bp 130 °C (0.1 mmHg), which crystallized as long needles: mp 49–50 °C; ^1H NMR ($CDCl_3$) δ 0.78–1.08 (m, 6 H, CH_2CH_3), 1.37–1.89 (m, 4 H, CH_2CH_3), 2.35 (s, 3 H, Ar CH_3), 3.19–3.46 (m, 4 H, NCH_2), 3.75 (s, 2 H, CH_2CO), 7.13–7.75 (m, 3 H (Ar); IR (neat) 1641, 1525, cm^{-1}. Anal. ($C_{16}H_{24}N_2O_3$) C, H, N.

2-Methyl-3-nitro-*N*,*N*-di-*n*-propylphenethylamine (8a). To a solution of 155.74 g (0.560 mol) of 7a in 1250 mL of anhydrous THF was added dropwise 848 mL of 1.0 M borane in THF. The mixture was refluxed for 1 h, an additional 150 mL of 1.0 M borane–THF was added, and this solution was stirred overnight. Anhydrous MeOH was added cautiously and the solution was concentrated in vacuo. The residual syrup was warmed on a steam bath with 6 N HCl (200 mL) for 1 h and then cooled and made basic with 40% NaOH. The oily product was taken into Et_2O, washed with brine, concentrated in vacuo, and distilled in a Kugelrohr flask to yield 123.94 g (83%) of thick oil: bp 115–120 °C (0.1 mmHg); ^1H NMR ($CDCl_3$) δ 0.89 (t, 6 H, CH_2CH_3), 1.22–1.70 (m, 4 H, CH_2CH_2), 2.34–2.98 (m, 8 H), 2.42 (s, 3 H, Ar CH_3), 7.08–7.66 (m, 3 H (Ar)). Anal. ($C_{15}H_{24}N_2O_2$) C, H, N.

2-Nitro-6-[2-(*N*,*N*-di-*n*-propylamino)ethyl]phenylpyruvic Acid (9a). Absolute EtOH, 0.89 g (0.0193 mol), was added dropwise to freshly cut K metal, 0.75 g (0.019 mol), in anhydrous Et_2O under a nitrogen atmosphere. Diethyl oxalate, 2.77 g (0.019 mol), was added dropwise with stirring after the metal had dissolved. After 10 min, 5.03 g (0.019 mol) of 9 was added dropwise. After an additional 10 min of stirring, the dark purple solution was allowed to stand overnight. The solution was concentrated with a stream of N_2 and 100 mL of H_2O was added (pH 10). The solution was extracted with Et_2O, and after drying ($MgSO_4$), the ether was removed to provide 2.59 g of crude unreacted starting material 8a. The H_2O layer was diluted with 300 mL of H_2O and acidified to pH 1.5 with 3 N HCl. The tan precipitate was separated and crystallized from HOAc: 3.37 g (52%), mp 220–225 °C; ^1H NMR (D_2O–DCl) δ 0.85 (t, 6 H, CH_2CH_3), 1.35–1.85 (m, 4 H, 2.90–3.27 (m, 8 H, 7.20–7.79 (m, 3 H (Ar)); IR (Nujol) 1740, 1710, 3450 cm^{-1}. Anal. ($C_{17}H_{24}N_2O_5 \cdot 0.25\ H_2O$) C, H, N.

2-Nitro-6-[2-(di-*n*-propylamino)ethyl]phenylacetic Acid Hydrochloride (10a). To a cold (10 °C) mixture of 26.0 g (0.0773 mol) of 9a in 400 mL of 2% NaOH (0.20 mol) was added 13.7 mL (0.159 mol) of 30% H_2O_2. After addition was completed the solution was brought to room temperature and stirred for 1 h.

(27) Kende, A. S.; Hodges, J. C. *Synth. Commun.* **1982**, *12*, 1–10.
(28) Teitel, S.; O'Brien, J. P. *J. Org. Chem.* **1976**, *41*, 1657–1658.
(29) Askam, V.; Deska, R. H. L. *J. Chem. Soc. C* **1969**, 1935–1936.

The pH was adjusted to 1.5 by careful addition of concentrated HCl. The volume was reduced in vacuo and the solution cooled to room temperature to give 18.5 g of 10a. A second crop, 2.77 g, was obtained when the filtrate was cooled overnight at 10 °C; total yield 21.26 g (80%), mp 188–192 °C: ^{1}H NMR (D_2O) δ 0.89 (t, 6 H, CH_2CH_3), 1.42–1.92 (m, 4 H, CH_2CH_3), 3.00–3.50 (m, 8 H), 3.99 (s, 2 H, (CH_2CO)), 7.30–7.89 (m, 3 H (Ar)). Anal. ($C_{15}H_{21}N_2O_4$·HCl) C, H, N.

4-[2-(Di-*n*-propylamino)ethyl]-2(3*H*)-indolone Hydrochloride (28). A mixture of 2.0 g (0.0058 mol) of 10a and 0.205 g of 5% Pd/C catalyst in 100 mL of EtOH was hydrogenated at room temperature and 50 psi for 5 h. The catalyst was removed and the solution concentrated in vacuo to a white powder. Crystallization from 400 mL of CH_3CN gave 28, which was identical in all respects with material prepared via Scheme I.

4-Methoxy-*N*-*n*-propylphenethylamine Hydrochloride (6). Reaction of 50 g (0.32 mol) of 4-methoxybenzeneethanamine and 31.5 g (0.31 mol) of propionyl chloride was carried out as described for 7a to give 56.5 g (82%) of white crystalline *N*-[2-(4-methoxyphenyl)ethyl]propanamide, mp 75–77 °C. Crystallization of a small sample from CH_2Cl_2–hexane gave crystals, mp 78–79.5 °C. Anal. ($C_{12}H_{17}NO_2$) C, H, N. Reduction of 50.0 g (0.24 mol) of the amide was carried out as described for 8a to give 43.4 g (79%) of white crystalline hydrochloride, mp 209–211 °C after recrystallization from EtOH–Et_2O. Anal. ($C_{12}H_{19}NO$·HCl) C, H, N.

N-(4-Methoxyphenethyl)-*N*-(2-methyl-3-nitrophenethyl)-*N*-*n*-propylamine (8b). The reaction of 23.5 g (0.10 mol) of 6 with the acid chloride prepared from 20 g (0.102 mol) of 2-methyl-3-nitrophenylacetic acid was carried out essentially as described for the preparation of 7a to give the crude amide as an oil, which was used without further purification. It was reduced with borane in THF as described for 8a to give 27.4 g (79.5%) of 8b as an amber oil after Kugelrohr distillation (bp 200 °C (1.5 mmHg)). Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

2-Nitro-6-[2-[*N*-(4-methoxyphenethyl)-*N*-*n*-propylamino]ethyl]phenylacetic Acid Hydrochloride (10b). This Reissert reaction was carried out with 10.0 g (0.028 mol) of 8b by using the procedure described for the preparation of 9a to give 5.3 g (41.7%) of the crude hydrochloride of the phenylpyruvic acid as a buff powder. It melted at 174 °C dec after crystallization from EtOAc. A total of 5.6 g (56%) of crude unreacted starting material was also obtained. A total of 8.3 g (0.018 mol) of the crude phenylpyruvic acid was converted to the acetic acid as described for 10a. The hydrochloride of the acetic acid was soluble in $CHCl_3$ and the crude product was isolated as a foam (8.2 g) by concentrating a solution of the hydrochloride in $CHCl_3$. An analytical sample, mp 114–119 °C dec, was obtained by concentrating to dryness a CH_2Cl_2 solution of the sodium salt and trituration with a small volume of dilute HCl. Anal. ($C_{22}H_{28}N_2O_5$·HCl·0.5H_2O) C, H, N.

4-[2-[*N*-(4-Methoxyphenethyl)-*N*-*n*-propylamino]-ethyl]-2(3*H*)-indolone Hydrochloride (33) and 1-Hydroxy-4-[2-[*N*-(4-methoxyphenethyl)-*N*-*n*-propylamino]ethyl]-2-(3*H*)-indolone Hydrochloride (35). A mixture of 6.2 g (0.014 mol) of crude 10b, 350 mL of EtOH, 2 mL of concentrated HCl, and 700 mg of 5% Pd/C catalyst was hydrogenated at room temperature and 50 psi for 6 h. After removal of the catalyst, the solvent was removed in vacuo. Column chromatography (silica gel 60, 150 g, 70–230 mesh, E. Merck) using $CHCl_3$–MeOH (95:5) and collecting 40-mL fractions gave 1.04 g of 33 and 1.8 g of 35 as powders.

N-[2-[4-[(Hydroximinoacetyl)amino]phenyl]ethyl]-2,2,2-trifluoroacetamide (12). Amine 11[30] (9.77 g, 0.042 mol), dissolved (80 °C) in 190 mL of H_2O containing 50 mL of H_2SO_4, was reacted with chloral hydrate (7.2 g, 0.044 mol) and hydroxylamine sulfate (20.98 g, 0.128 mol) as described in the preparation of 4. Buff crystals of 12 were obtained upon cooling, 7.9 g (62%). An analytical sample, mp 175–176 °C, was obtained by crystallization from EtOAc–hexane. Anal. ($C_{12}H_{12}F_3N_3O_3$) C, H, N.

5-[2-(Trifluoroacetamido)ethyl]isatin (36). Compound 12 (7.9 g, 0.042 mol) was added rapidly in portions with stirring to 86 mL of concentrated H_2SO_4 at 80 °C. After 6 min the solution was poured over ice and the solid product extracted into EtOAc. The EtOAc solution was concentrated to 100 mL and cooled; 5.1 g of orange/red 36.

5-(2-Aminoethyl)-2(3*H*)-indolone Hydrochloride (38). Isatin 36 (2.62 g, 96.7 mmol) was catalytically reduced by method A used for the synthesis of 16 to give 37 as a white crystalline solid, mp 203–204 °C. A solution of 37 (0.5 g, 0.001 mol) in a mixture of 10 mL of 10% HCl and 10 mL of EtOH was refluxed for 16 h and concentrated to dryness in vacuo to give 38.

6-(2-Hydroxyethyl)-2(3*H*)-indolone Methanesulfonate (40). A solution of borane in THF (0.021 mol) was added with stirring to a suspension of 2.0 g (0.011 mol) of indolone-6-acetic acid[31] in 100 mL of THF. After the mixture was stirred for 16 h, 25 mL of MeOH was added, and the solvents were removed in vacuo. The residue was again stirred with a small volume of MeOH and concentrated in vacuo to give a pale green solid. Chromatography on 106 g of silica gel 60 (70–230 mesh, E. Merck) with a MeOH–$CHCl_3$ gradient and elution with 20% MeOH–$CHCl_3$ gave 1.04 g (46%) of 6-(2-hydroxyethyl)-2(3*H*)-indolone. To a solution of 1.0 g (0.0057 mol) of this carbinol in 5 mL of pyridine was added 0.55 g (0.0057 mol) of methanesulfonyl chloride in one portion with ice cooling. This solution was stirred at room temperature for 2 h and then poured into dilute HCl and extracted with CH_2Cl_2. The CH_2Cl_2 solution was extracted with 10% HCl and brine and then dried ($MgSO_4$). Removal of the CH_2Cl_2 gave 1.12 g of 40 as a pale orange solid.

5-[2-(Di-*n*-propylamino)ethyl]-2(3*H*)-indolone Hydrochloride (41). A solution of mesylate 40 (0.88 g, 0.0035 mol) in a mixture of 8.8 mL of MeOH and 8.8 mL of di-*n*-propylamine was stirred in a sealed vessel at 100 °C for 2.5 h. The volatile liquids were removed in vacuo, H_2O was added, and the mixture was made alkaline with 10% NaOH and extracted with ether. Addition of HCl gas to the ether solution gave pink crystals of 41.

4-Methoxy-*N*,*N*-di-*n*-propylphenethylamine (42). To a solution of 30 g (0.3 mL) of di-*n*-propylamine in 70 mL of $CHCl_3$ was added at 0 °C a solution of 18.4 g (0.1 mol) of 4-methoxyphenylacetyl chloride in 70 mL of $CHCl_3$. The mixture was heated at 50 °C for 2 h and then concentrated in vacuo. The residue was dissolved in $CHCl_3$ and extracted with 10% HCl, 5% Na_2CO_3, and H_2O. After drying ($MgSO_4$), the $CHCl_3$ was removed in vacuo to give 23.8 g (95%) of crude amide as a viscous oil, which was used without further purification. To a solution of 0.98 M diborane in THF (750 mL, 0.735 mol) was added with stirring a solution of 127.2 g (0.51 mol) of crude amide in 300 mL of THF. The mixture was refluxed for 4 h, and after cooling, 50 mL of MeOH was added and stirring was continued for 60 h. The solvents were removed in vacuo, and the oily yellow residue was heated with dilute (10%) HCl on the steam bath for 2 h. This solution was cooled and extracted with Et_2O and the aqueous phase was made basic with 40% NaOH. The oily product was extracted into Et_2O, and after drying ($MgSO_4$), the ether was removed in vacuo to give 101 g of yellow oil. Distillation at 0.5 mm gave 90.3% (75%) of clear oil, bp 113–116 °C. Anal. ($C_{15}H_{25}NO$) H, N, C: calcd, 76.55; found, 75.70.

4-Hydroxy-3-nitro-*N*,*N*-di-*n*-propylphenethylamine (44). To a solution of 20 g (0.095 mol) of 43 in 150 mL of HOAc was added with stirring 8.42 g (5.97 mL, 0.095 mol) of 70–71% HNO_3. The solution was stirred overnight at room temperature, then diluted with water and neutralized with NH_4OH. The oily product was extracted into EtOAc. Purification using dry column chromatography (silica gel, 10% MeOH–EtOAc) gave 11.8 g of a dark amber oil, which crystallized on standing.

3-Amino-4-(benzyloxy)-*N*,*N*-di-*n*-propylphenethylamine Dihydrochloride (45). A mixture of 23.5 g (0.088 mol) of 44, 40 g (0.29 mol) of K_2CO_3, and 10.5 mL (15.1 g, 0.088 mol) of benzyl bromide in 500 mL of acetone was refluxed for 2 h. After filtration, the acetone was removed in vacuo and the residue dissolved in warm EtOAc and cooled. A small amount of quaternary salt was removed by filtration and the filtrate concentrated in vacuo to give 30.2 g of an orange oil. Purification by dry column chro-

(30) Foye, W. O.; Anderson, J. C. *J. Pharm. Sci.* 1969, *58*, 1658–1660.

(31) Ruggli, P.; Bussemaker, B. B.; Müller, W. *Helv. Chim. Acta* 1935, *18*, 613–623.

matography (silica gel, 50% Et_2O–petroleum ether) gave 23.1 g (73.5%) of 4-(benzyloxy)-3-nitro-*N*,*N*-di-*n*-propylphenethylamine, which was used without further purification. To a solution of the 23.1 g (0.065 mol) of the above nitro compound in 100 mL of MeOH was added 0.35 g of PtO_2 and sufficient dry HCl gas in Et_2O to partially neutralize the amine. The mixture was hydrogenated at 60 psi with shaking. The catalyst was removed by filtration and the solvent by evaporation in vacuo. The residue was dissolved in *i*-PrOH and made acidic by the addition of ethereal HCl, Et_2O was added slowly, and the salt was filtered; 24.8 g (98%, 71% overall).

3-Formamido-4-hydroxy-*N*,*N*-*n*-dipropylphenethylamine Hydrochlorides (46). A solution of 5.0 g (0.015 mol) of the free base of 45 in 150 mL of ethyl formate was refluxed overnight. The ethyl formate was removed in vacuo and the residual oil dissolved in EtOAc/Et_2O. A small amount of white solid was removed by filtration, and the solvents were again removed in vacuo. This crude product (5.2 g) was used without further purification. A solution of 1.75 g (0.0049 mol) of the above crude formyl derivative in 50 mL of MeOH containing a small amount of EtOAc was hydrogenated at 60 psi with shaking in the presence of 0.75 g of 10% Pd/C. After 1 h the catalyst was removed by filtration and the solvents were removed by evaporation in vacuo to give 1.3 g of an oily product. It was converted to the hydrochloride salt by the addition of ethereal HCl to a solution in MeOH, 0.925 g.

3-Acetamido-4-hydroxy-*N*,*N*-di-*n*-propylphenethylamine Hydrochloride (47). A solution of 2.1 g (0.0054 mol) of the free base of 45 in 75 mL of Ac_2O was stirred overnight at room temperature. The Ac_2O was removed in vacuo to give 2.4 g of a tan oil. This oil was dissolved in a mixture of 50 mL of MeOH and 10 mL of EtOAc and hydrogenated with shaking at 60 psi in the presence of 1.0 g of 10% Pd/C. The catalyst was filtered and the filtrate was concentrated to an oil in vacuo. This was converted to the hydrochloride in methanol with use of ethereal HCl, 1.75 g.

Assay for Inhibition of Adrenergic Neurotransmission in the Isolated Perfused Rabbit Ear Artery (REA). A 2–4-cm segment of central ear artery is mounted in a narrow cylindrical chamber where it is simultaneously perfused intraluminally and superfused extraluminally with oxygenated Krebs solution. Drugs can be administered by means of either the intraluminal or extraluminal flow. Changes in arterial diameter are reflected as changes in intraluminal perfusion pressure. At 4-min intervals, the vascular sympathetic nerves are excited by pulses from an electronic stimulator delivered through platinum electrodes present in the chamber. The test drug is administered in increasing concentration. Each concentration is allowed to remain in contact with the tissue for 4 min. The drug concentration is increased immediately following the response to nerve stimulation. If the effect of dopaminergic blockade is to be determined (*S*)-sulpiride superfusion is begun after obtaining the initial concentration–effect curve for the test compound. Following a 30-min equilibration period, the curve is repeated in the presence of (*S*)-sulpiride.

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Registry No. 1, 81654-47-9; 2, 81654-48-0; 3, 81654-49-1; 4, 85763-09-3; 5, 101566-00-1; 6-HCl, 101566-01-2; 7a, 91374-22-0; 8a, 91374-23-1; 8b, 101566-02-3; 9a, 97351-95-6; 10a, 91374-25-3; 10b, 101566-03-4; 11, 24954-62-9; 12, 101566-04-5; 13, 101566-05-6; 14, 81654-50-4; 14, 81654-50-4; 15, 101566-06-7; 16, 101566-07-8; 17-HCl, 101566-08-9; 18, 101566-09-0; 18-HBr, 101566-10-3; 19, 81654-51-5; 20, 81654-52-6; 21, 81654-54-8; 21-HCl, 81654-53-7; 22, 85763-08-2; 22-HBr, 81654-59-3; 23-HCl, 101566-11-4; 24, 101566-12-5; 24-HBr, 101566-13-6; 25, 85763-10-6; 25-HCl, 81654-56-0; 26, 81654-62-8; 26-HBr, 81654-57-1; 27-HCl, 91374-19-5; 28, 91374-21-9; 28-HCl, 91374-20-8; 29-HCl, 101566-14-7; 30, 101566-15-8; 31, 101566-16-9; 31-HBr, 101566-17-0; 32, 101566-18-1; 33, 101566-19-2; 33-HCl, 101566-20-5; 34, 101566-21-6; 34-HBr, 101566-22-7; 35-HCl, 101566-23-8; 36, 101566-24-9; 37, 101566-25-0; 38, 101566-26-1; 38-HCl, 101566-27-2; 39, 101566-28-3; 39-HCl, 101566-29-4; 40, 101566-30-7; 41, 101566-31-8; 41-HCl, 101566-32-9; 42, 95886-45-2; 43-HBr, 101566-33-0; 44, 95886-47-4; 45-2HCl, 95886-48-5; 46, 101566-34-1; 46-HCl, 101566-35-2; 47, 101566-36-3; 47-HCl, 101566-37-4; 4-methoxybenzeneethenamine, 55-81-2; propionaldehyde, 123-38-6; 1,2-ethanedithiol, 540-63-6; 4-methylphenylacetaldehyde, 5703-26-4; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4; 2-methyl-3-nitrophenylacetic acid, 23876-15-5; 4-methoxybenzeneethenamine, 55-81-2; propionyl chloride, 79-03-8; *N*-[2-(4-methoxyphenyl)ethyl]propanamide, 67191-51-9; phenylpyruvic acid, 156-06-9; 6-(2-hydroxyethyl)-2(3*H*)-indolone, 101566-38-5; 4-methoxyphenylacetyl chloride, 4693-91-8; 4-(benzyloxy)-3-nitro-*N*,*N*-di-*n*-propylphenethylamine, 96886-51-0.

Synthesis, Saludiuretic, and Antihypertensive Activity of 6,7-Disubstituted 1(2*H*)- and 3,4-Dihydro-1(2*H*)-phthalazinones

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The synthesis of the isomeric series 6-chloro-7-sulfamoyl- and 7-chloro-6-sulfamoyl-1(2*H*)-phthalazinones (1 and 2) and 6-chloro-7-sulfamoyl- and 7-chloro-6-sulfamoyl-3,4-dihydro-1(2*H*)-phthalazinones (3 and 4), combining structural features characteristic to furosemide and hydralazine, is described, the mechanism of the formation of 1 and 2 is discussed, and their structure–activities relationships are studied. Preliminary screening in the rat shows that series 1 and 3 exhibit diuretic and saluretic activity similar to that of chlorothiazide with, however, Na^+/K^+ ratios more favorable than chlorothiazide and furosemide. The compounds of series 2 and 4 are practically inactive. All four series show initial antihypertensive activity lower than that of hydralazine. However, compounds 1a, 1c, and 4a show a higher activity at 8 and/or 24 h after administration and thus may offer a unique combination of a "loop" diuresis with direct long-acting peripheral vasodilating effects.

Many diuretics and saluretics possess an aromatic nucleus with a halogen, pseudohalogen, or a phenoxy group in the position ortho to and an electronegative group in the position meta to a sulfonamide group.[1] Among those that have found wide use are furosemide (5), chlorothiazide (6), hydrochlorothiazide (7), and bumetanide (15) (Figure 1).

Compounds having cyclic or exocyclic –N–N– moieties (hydralazine, dihydralazine, compounds 11–14[2–4]) are

(1) Feit, P. *J. Med. Chem.* 1971, *14*, 432.

(2) Kikuo, A.; Kiyoshi, S. Jpn. Patent 7455680; *Chem. Abstr.* 1974, *81*, 136167).

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REDACTED

EXHIBIT J

REDACTED

REDACTED

EXHIBIT K

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EXHIBIT L

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